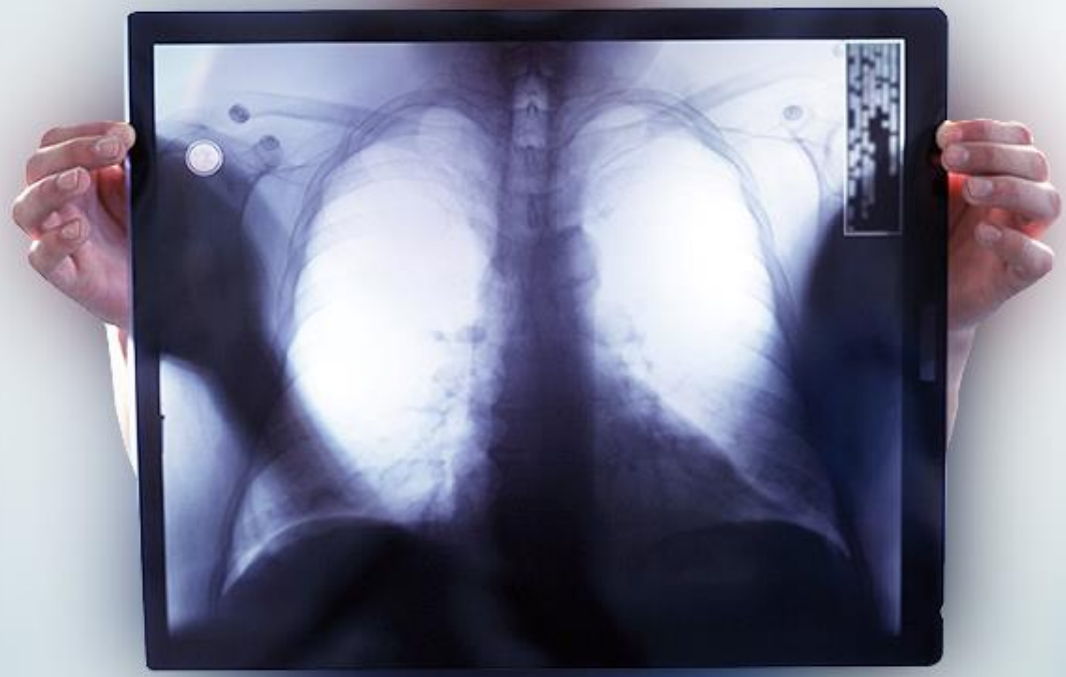
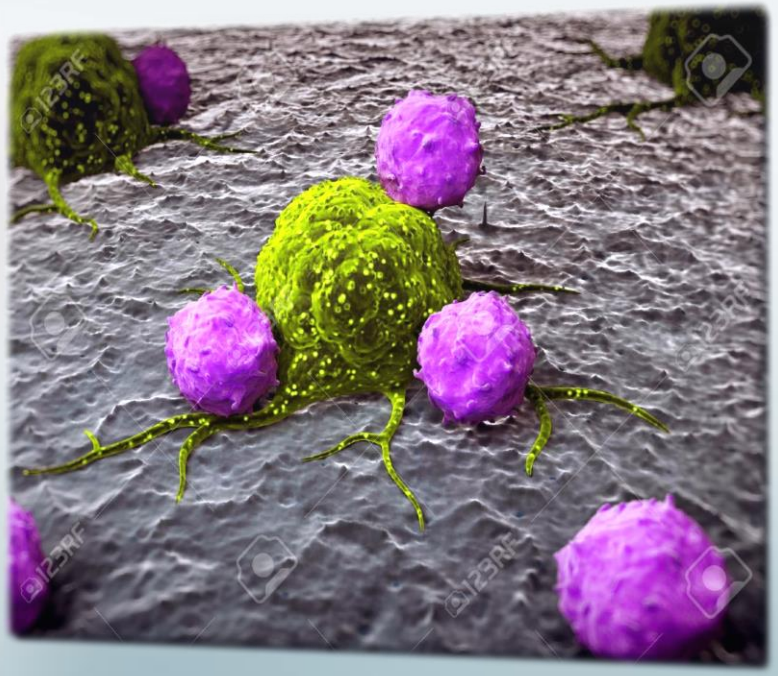
Ανοσοθεραπεία του καρκίνου του Πνεύμονα

Πνευμονική τοξικότητα της ανοσοθεραπείας και αντιμετώπιση





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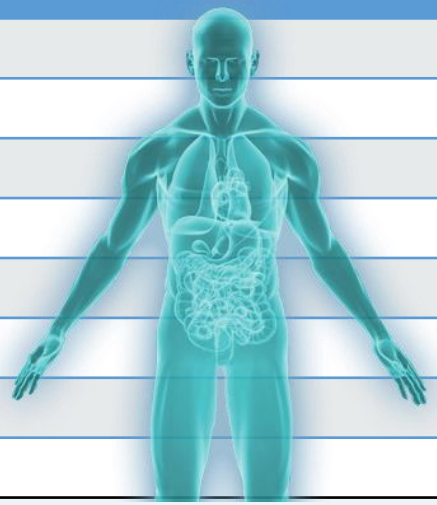
Γ.Ν.Ν.Θ.Α. «Η Σωτηρία»

Organs Systems Often Affected by I-O Therapy-Related AEs

I-O therapy-associated AEs target certain organ systems[1]
Skin[1–6]
Endocrine system[2,4,6,7–10]
Liver[2,6,11–12]
Gastrointestinal tract[2,6,9,13]
Nervous system[6,10,14,15]
Eyes[1,4,16–18]
Respiratory system[1,5,6,10,15,19]
Hematopoietic cells[6,9,12,20–22]



1. Amos SM, et al. *Blood.* 2011;118:499–509; 2. Phan GQ, et al. *PNAS.* 2003;100:8372–8377; 3. Rosenberg SA. *J Immunother Emphasis Tumor Immunol.* 1996;19:81–84; 4. Chianese-Bullock KA, et al. *J Immunother.* 2005;28:412–419; 5. Harris J, et al. *Med Pediatr Oncol.* 1994;22:103–106; 6. Chow LQ. *Am Soc Clin Oncol Educ Book*. 2013:280–285; 7. Bendle GM, et al. *Nat Med.* 2010;16:565–570; 8. Soni N, et al. *Cancer Immunol Immunother.* 1996;43:59–62; 9. Ronnblom LE, et al. *Ann Intern Med.* 1991;115:178–183; 10. Fraenkel PG, et al. *J Immunother.* 2002;25:373–378; 11. Lamers CH, et al. *J Clin Oncol.* 2006;24:e20–e22; 12. Roskrow MA, et al. *Leuk Res.* 1999;23:549–557; 13. Parkhurst MR, et al. *Mol Ther.* 2011;19:620–626; 14. Pellkofer H, et al. *Brain.* 2004;127:1822–1830; 15. Smalley RV, et al. *Blood.* 1991;78:3133–3141; 16. Dudley ME, et al. *J Clin Oncol.* 2008;26:5233–5239; 17. Yeh S, et al. *Ophthalmology*. 2009;116:981–989; 18. Robinson MR, et al. *J Immunother*. 2004;27:478–479; 19. Morgan RA, et al. *Mol Ther.* 2010;18:843–851; 20. Kochenderfer JN, et al. *Blood.* 2010;116:4099–4102; 21. Lin TS, et al. *J Clin Oncol.* 2010;28:4500–4506; 22. Herishanu Y, et al. *Leuk Lymphoma.* 2003;44:2103–2108.

Toxicities of Checkpoint Immunotherapies

Drug	Pneumonitis	Colitis, Diarrhea (Entercolitis[a])	Rash, Pruritus (Dermatitis[a])
Ipilimumab 3 mg/kg 10 mg/kg	<1%	8%, 32-46% (7%) 16%, 49% (16%)	29-42%, 31% (2%) 50%, 45% (4%)
Nivolumab	3.1%	2.9%, 23-31%	21-40%, 17-23%, (9%)
Ipilimumab + Nivolumab	6%	26%, 52%	53%, NR (23%)
Pembrolizumab	3.4%	1.7%, 14-26%	17-24%, 11-28%
Atezolizumab	2.6%	19.7%	15%[a]

[a]Grade 3-5, immune-mediated
[b]Urothelial carcinoma
Ipiliumab prescribing information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125377s073lbl.pdf
Nivolumab prescribing information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125554s022lbl.pdf
Pembrolizumab prescribing information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s012lbl.pdf
Atezolizumab prescribing information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761041s000lbl.pdf

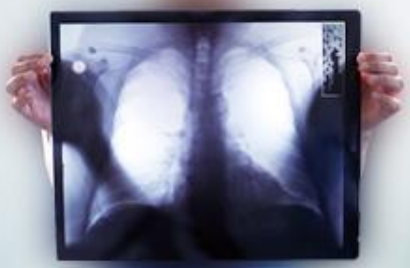
Clinical Cancer Research

Personalized Medicine and Imaging

PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course

Mizuki Nishino, Nikhil H Ramaiya, Mark M Awad, Lynette M Sholl, Jennifer A Maattala, Myriam Taibi, Hiroto Hatabu, Patrick A. Ott, Philippe Armand, and F. Stephen Hodi

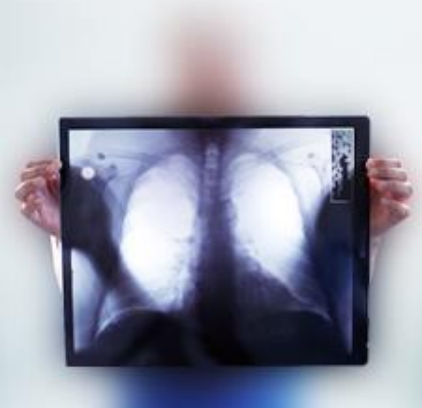
DOI: 10.1158/1078-0432.CCR-16-1320 Published 17 August 2016



Dana Farber Cancer Institute

- Advanced melanoma, lung cancer, or lymphoma
- Treated with Nivolumab
- Developed pneumonitis

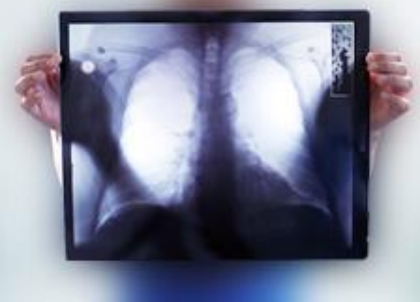
- ClinicalTrials.gov Identifiers:
- NCT00730639, NCT01721746, NCT01714739, NCT01783938, NCT01928394, NCT02186249, NCT01592370, NCT02038933, NCT02038946, NCT02181738



Results

- 170 patients treated with Nivo
- 74 Monotherapy
- 96 Combination with other checkpoint inhibitor (ipilimumab – lirilumab)

- 20 patients (11.8%) developed pneumonitis
- 5 patients received nivolumab monotherapy
- 15 patients received combination therapy



Severity of pneumonitis

- Grade 1 : 5 patients (25%)
- Grade 2 : 10 patients (50%)
- Grade 3 : 5 patients (25%)

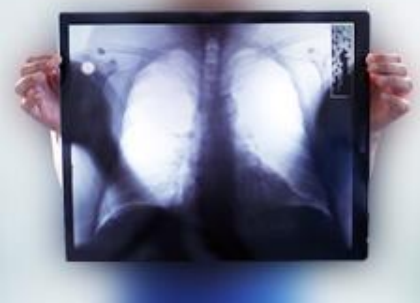
Symptoms

- Cough in 12 patients (60%)
- Dyspnea in 11 patients (55%)

Median time to pneumonitis

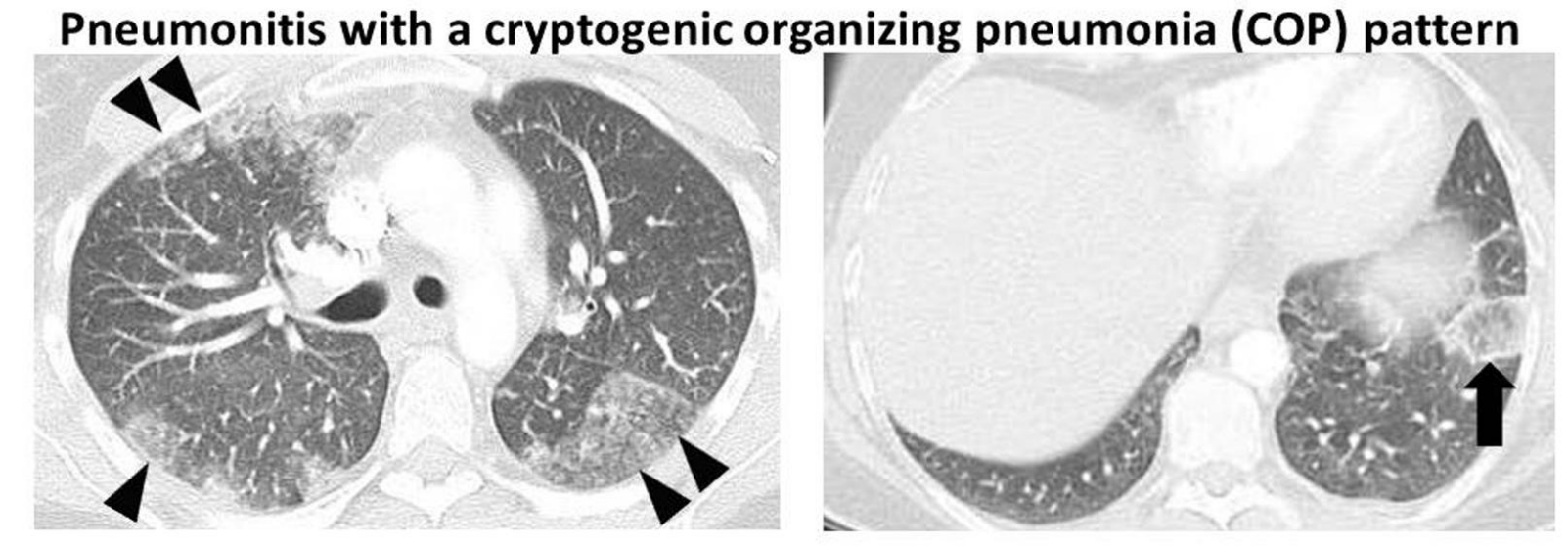
- 2.6 months (range: 0.5-11.5)

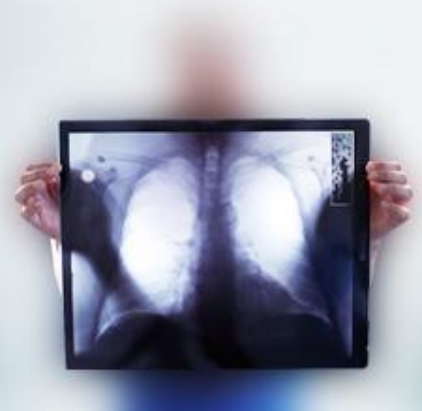
- 4 lung cancer patients VS 16 melanoma and lymphoma
- median time to pneumonitis:
- 1.1 vs. 3.1 months (p=0.008).



Radiographic patterns of pneumonitis

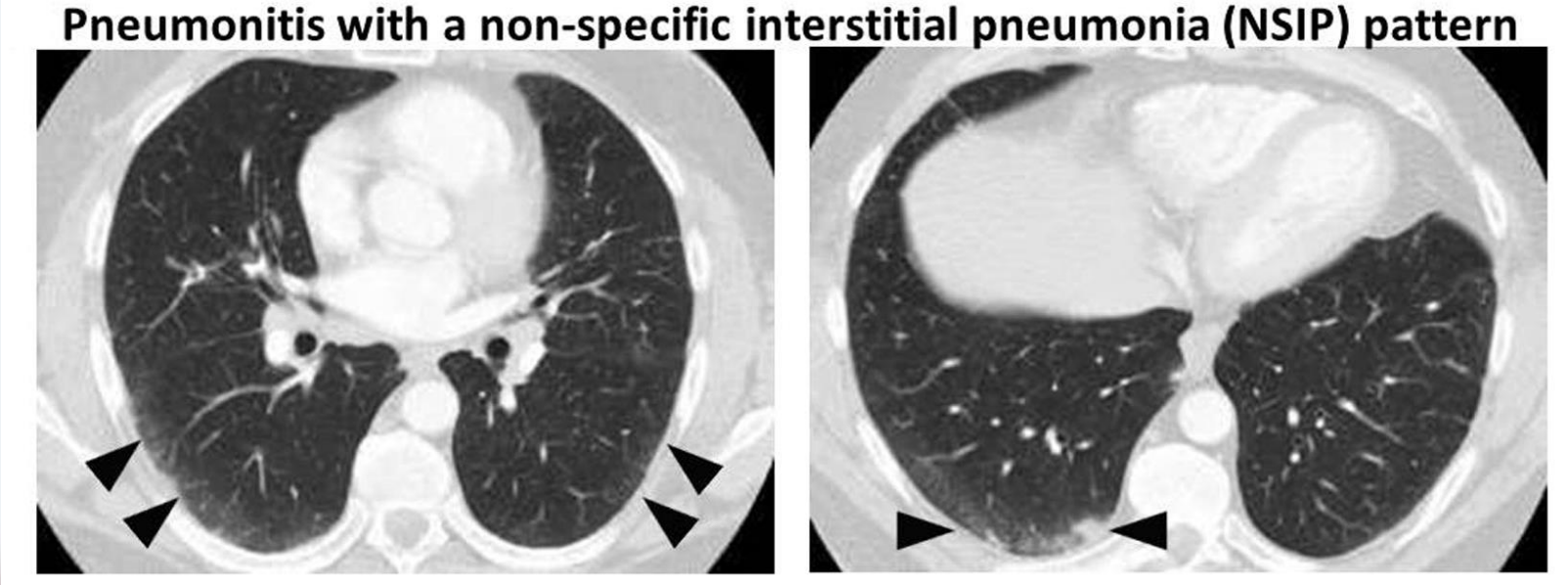
COP Pattern – most common (65%) – Grade 2





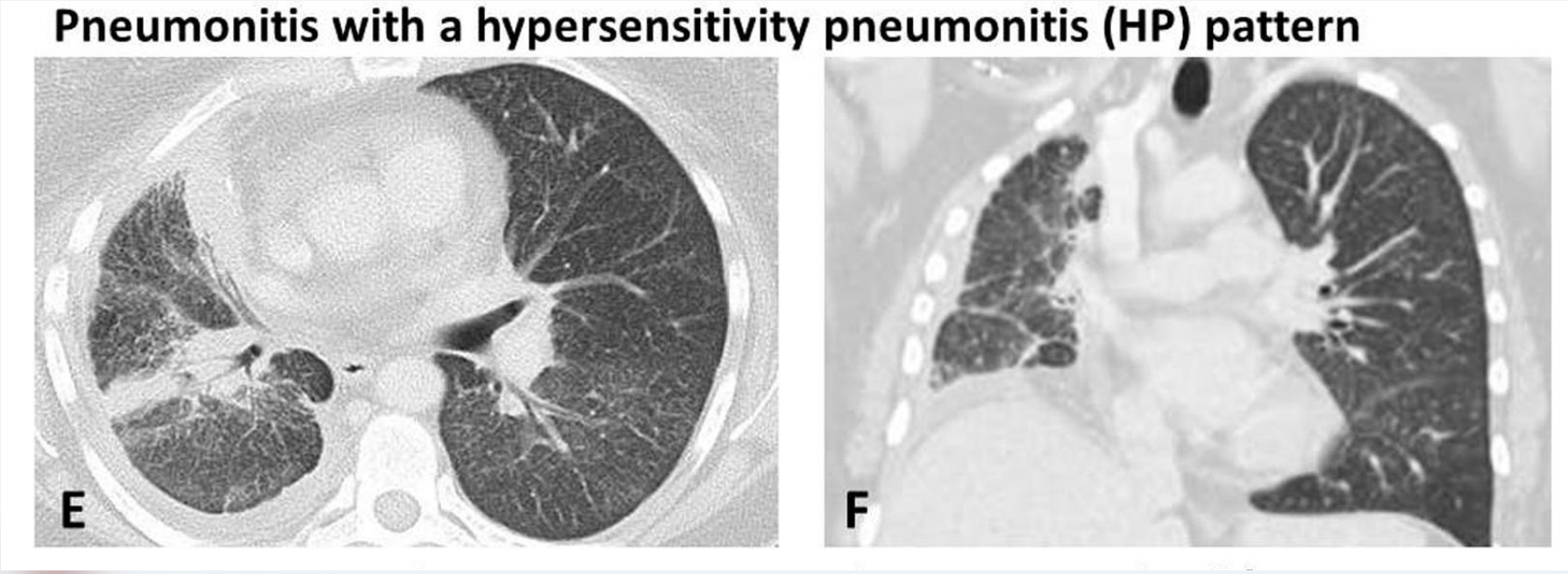
Radiographic patterns of pneumonitis

NSIP Pattern 15% - Grade 1



Radiographic patterns of pneumonitis

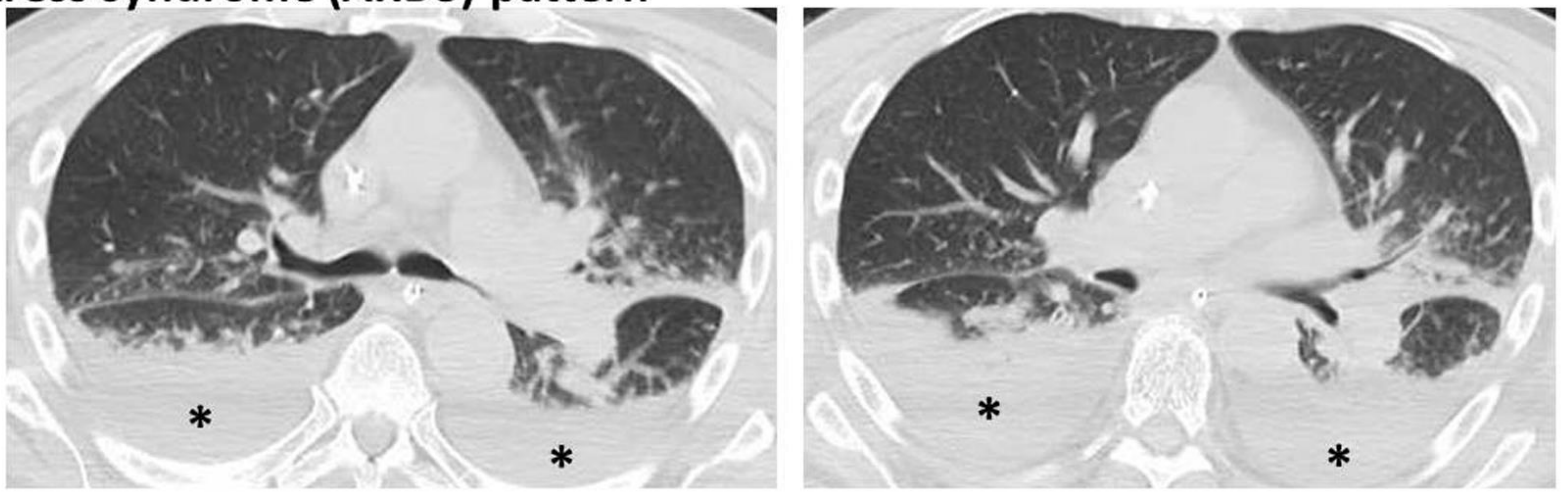
HP Pattern 10% - Grade 1



Radiographic patterns of pneumonitis

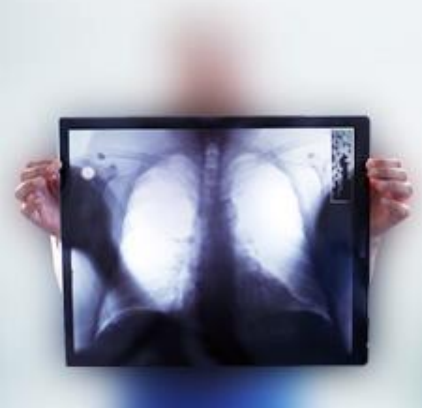
AIP-ARDS Pattern 10% - Grade 3

Pneumonitis with an acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern



Radiographic patterns of pneumonitis

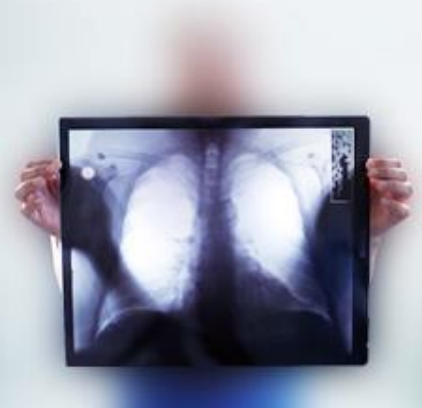
- No significant differences between monotherapy and combination therapy
- No significant differences among different tumor types
- Mixed - multifocal distribution was most common
- All lung lobes were involved in 75% of the patients



TREATMENT

- Withhold Immunotherapy (100%)
- Corticosteroids (17/20 – 85%)
- Median Cort therapy : 6.1 weeks tappering
- Infliximab (3/17 – 15%)

- Hospital admission (7 pt – 3 M, 4 LC)
- Death 1pt

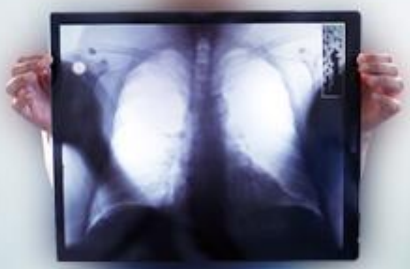


Immunotherapy Rechallenge

- 7 patients:

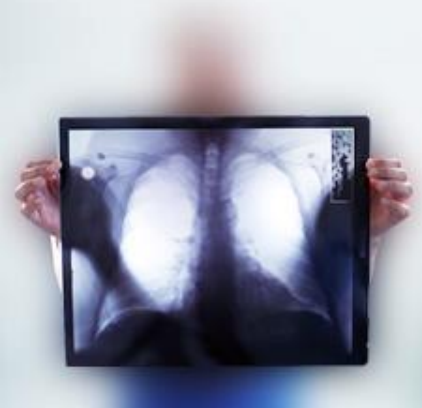
- 4 Monotherapy
- 3 Combination

- 2 patients with recurrent Pneumonitis
  (1 patient with pneumonitis flare)



Conclusion

- PD-1 inhibitor-related pneumonitis showed a spectrum of radiographic patterns
- Most cases were responsive to corticosteroids
- One-third of the patients were able to restart nivolumab therapy
- Few patients experienced recurrent pneumonitis during retreatment
- Importance of increased awareness of the entity for the early diagnosis and treatment
- Need for multidisciplinary approach



JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

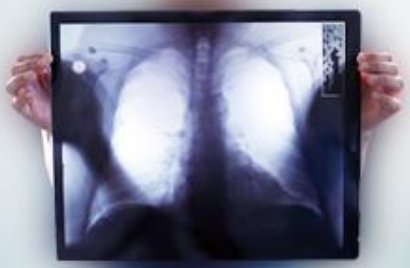
Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy

Jarushka Naidoo, Xuan Wang, Kaitlin M. Woo, Tunc Iyriboz, Darragh Halpenny, Jane Cunningham, Jamie E. Chaft, Neil H. Segal, Margaret K. Callahan, Alexander M. Lesokhin, Jonathan Rosenberg, Martin Voss, Charles M. Rudin, Hira Rizvi, Xue Hou, Katherine Rodriguez, Melanie Albano, Ruth-Ann Gordon, Charles Leduc, Natasha Rekhtman, Bianca Harris, Alexander M. Menzies, Alexander D. Guminski, Matteo S. Carlino, Benjamin Y. Kong, Jedd D. Wolchok, Michael A. Postow, Georgina V. Long, and Matthew D. Hellmann

Published online ahead of print at www.jco.org on September 19, 2016

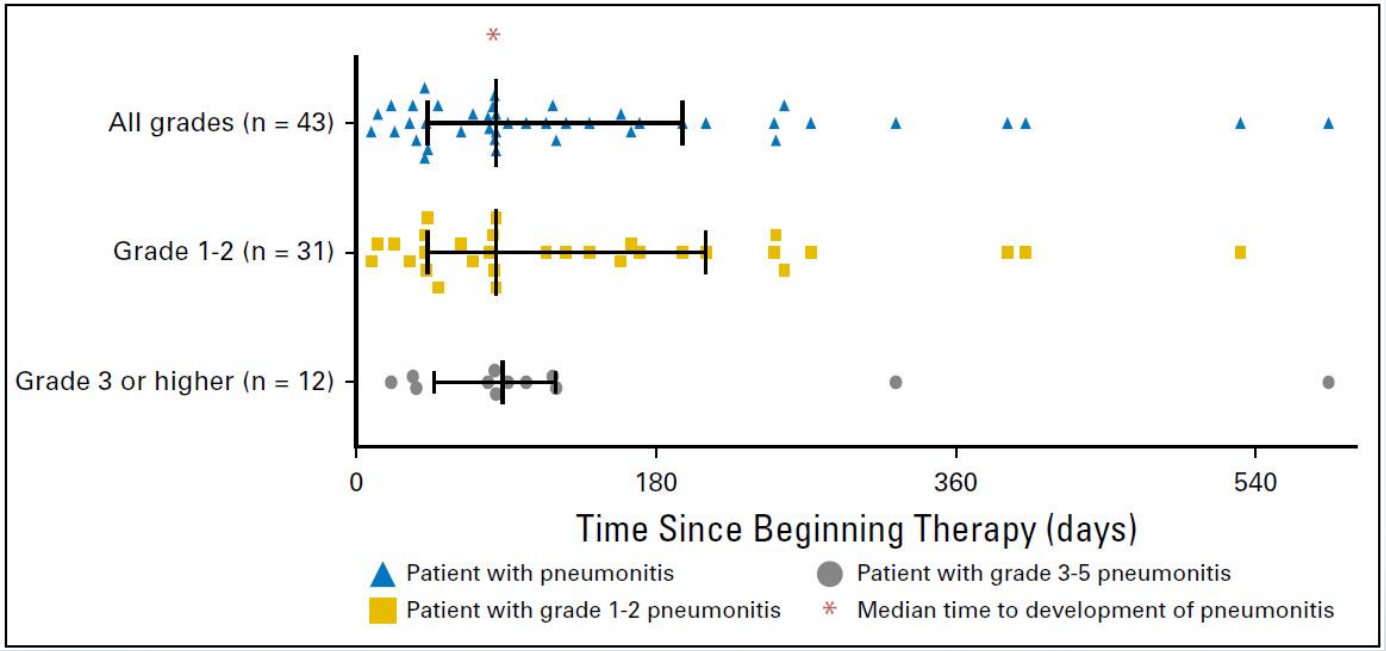
Patients and results

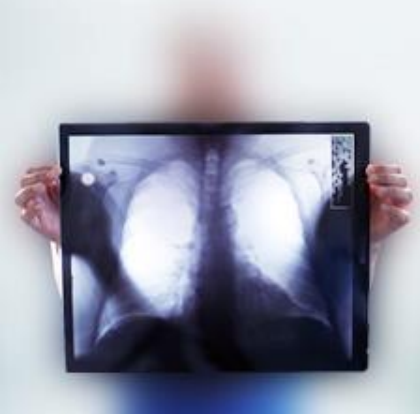
- Memorial Sloan Kettering Cancer Center: advanced solid cancers, 2009 to 2014
- Melanoma Institute of Australia: melanomas only, 2013 to 2015
- cases with confirmed malignant lung infiltration or infection were excluded
- 915 patients who received anti–PD-1/PD-L1mAbs, or in combination with anti–CTLA-4 mAb pneumonitis developed in 43 pt
- Incidence : 5%



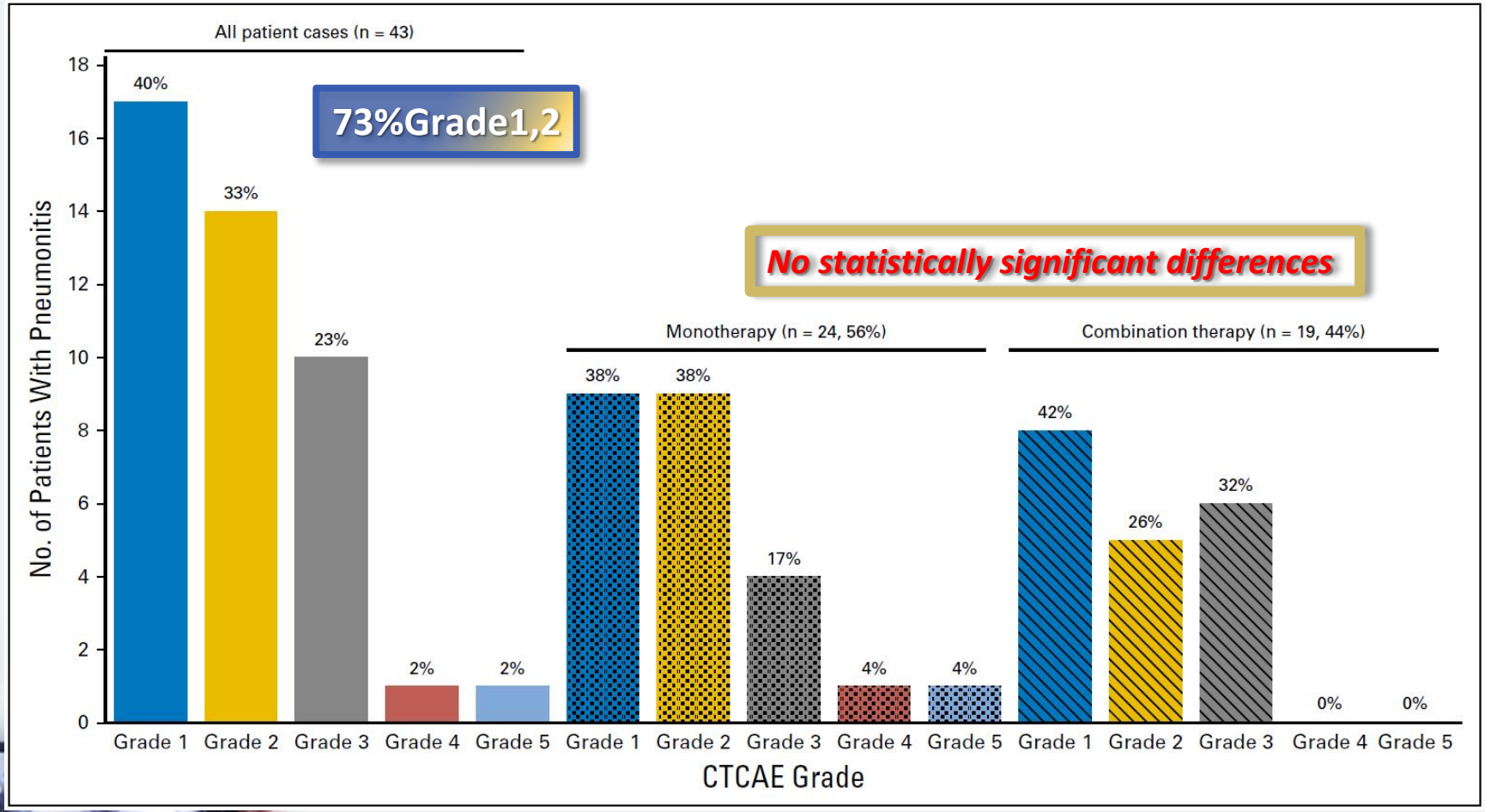
Onset of pneumonitis

- Median time to onset of pneumonitis : 2.8 months
- Range : 9 days to 19.2 months
- Combination therapy : Median time 2.7 m
- Monotherapy : Median time 4.6 m





GRADE

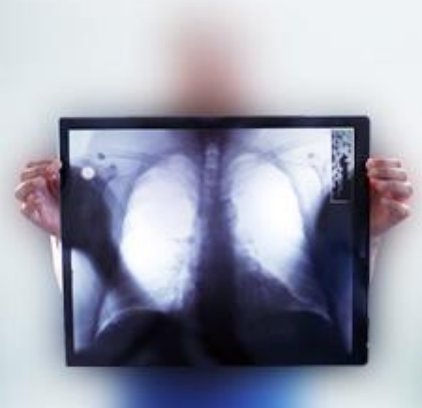

All patient cases (n = 43)
73%Grade1,2
No statistically significant differences
Monotherapy (n = 24, 56%)
Combination therapy (n = 19, 44%)
No. of Patients With Pneumonitis
CTCAE Grade
Grade 1
Grade 2
Grade 3
Grade 4
Grade 5
40%
33%
23%
2%
2%
38%
38%
17%
4%
4%
42%
26%
32%
0%
0%

Prevalence

- More frequent with Anti–PD-1/PD-L1 mAbs plus anti–CTLA-4 mAb vs anti–PD-1/PD-L1 monotherapy

- Anti–PD-1 vs anti–PD-L1 mAb

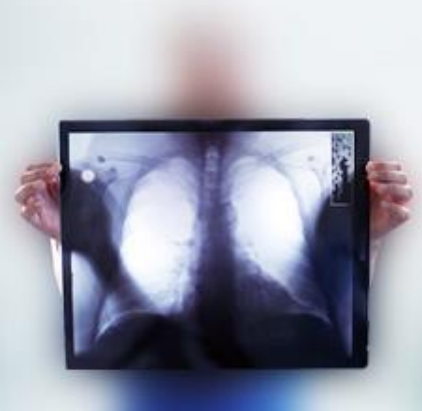
  Rates not statistically different



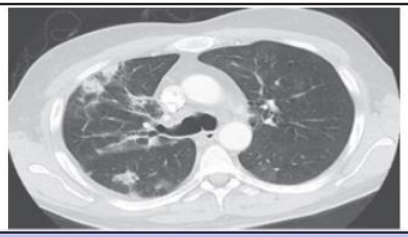
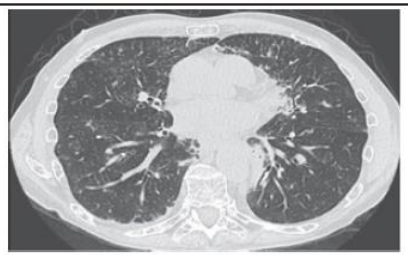
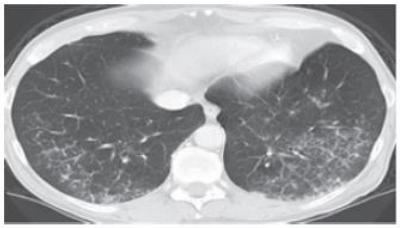
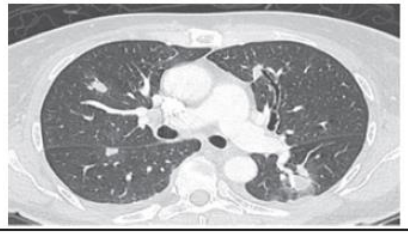
SYMPTOMS

SYMPTOMS	NO (%)
Dyspnea	23 of 43 [53%]
Cough	15 of 43 [35%]
Fever	5 of 43 [12%]
Chest pain	3 of 43 [7%]
Asymptomatic	**14 of 43 [33%]**

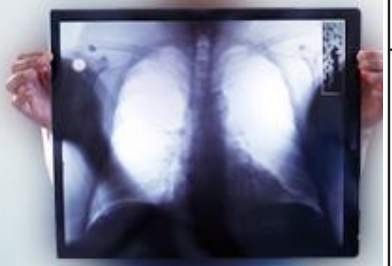
58% Additional immune-related toxicity (25 of 43)



Radiologic features

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

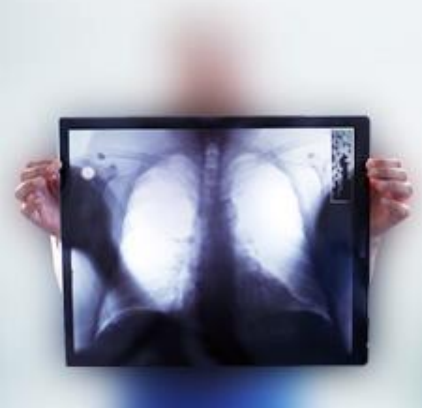
- COP – Like Appearance most common in NSCLC
- COP – Like more likely to require treatment



Radiologic features

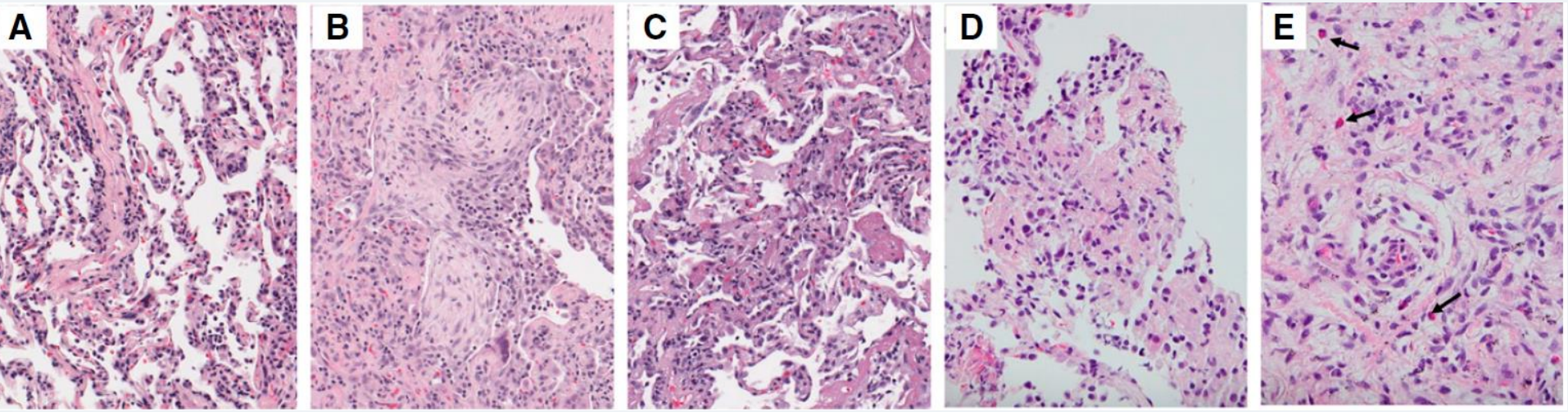
Chest X-Ray

- 67% : possible pneumonitis
- 11% : possible progressive cancer
- 22% : no new radiographic abnormality



Pathologic Features

- 11 pt Biopsy (8 bronchoscopic, 2 core biopsies,1 wedge resection)



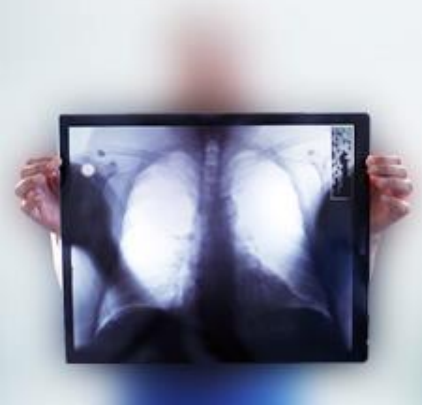
(A) Cellular interstitial pneumonitis

(B) Organizing pneumonia

(C) Diffuse alveolar damage

(D) Poorly formed granulomas

(E) Eosinophils (arrows).



Management and outcome

Highest CTCAE Grade	Highest Treatment Required for Pneumonitis Management, No. (%)				
	Treatment Hold	Oral Corticosteroids	Intravenous Corticosteroids	Additional Immunosuppression*	Total
1	15 (83)	2 (12)	0 (0)	0 (0)	17
2	0 (0)	10 (71)	4 (29)	0 (0)	14
3	0 (0)	2 (20)	4 (40)	4 (40)	10
4	0 (0)	0 (0)	1 (100)	0 (0)	1
5	0 (0)	0 (0)	0 (0)	1 (100)	1
Total	15	14	9	5	43

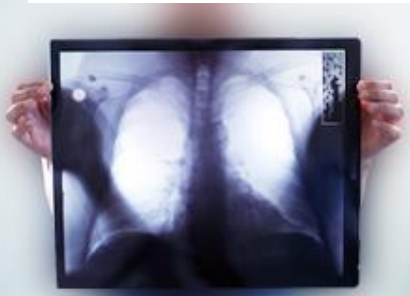
PNEUMONITIS FLAIR

	Clinical Outcomes of Pneumonitis Management, No. (%)				
	Completely Resolved	Improved	Worsened	Unknown	Total
1	17 (100)	0 (0)	0 (0)	0 (0)	17
2	10 (71)	3 (21)	0 (0)	1 (8)	14
3	4 (40)	2 (20)	4 (40)	0 (0)	10
4	1 (100)	0 (0)	0 (0)	0 (0)	1
5	0 (0)	0 (0)	1 (100)	0 (0)	1
Total	32	5	5	1	43

DEATH

3 INFECTION

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events (version 4).
*Additional immunosuppression: Three patients received infliximab alone (all grade 3), and two patients received both infliximab and cyclophosphamide (one grade 3 and one grade 5).



Oral corticosteroids as maximum immunosuppression used (14 of 17 [82%])

Median starting dose of prednisone :50 mg (range, 20 to 80 mg)

Median duration of corticosteroid: 68 days (range, 20 to 154 days)

Recurrent Pneumonitis

- 11 pt recurrent during corticosteroid therapy after improvement
- 8 improved with further management
- 3 worsened/died

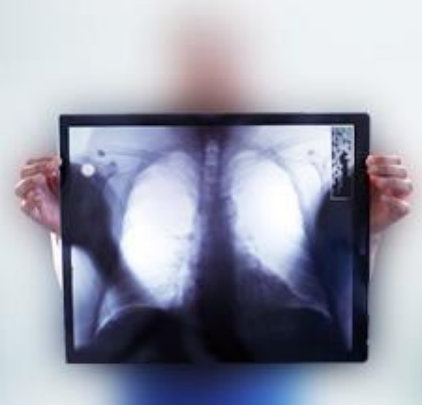
Rechallenge Immunotherapy

- 12/43 pt Rechallenge Immunotherapy
- 9 GR 1
- 3 GR 2

rechallenge →

1 pt → recurrent → Drug Holding

2 pt → recurrent → Corticosteroids



Clinical Features – Pneumonitis Outcomes

Worsening clinical outcome:

- Current vs former smokers (P = .053)
- Underlying lung conditions vs no lung conditions

- ❑ FEV1
- ❑ DLCO

→ NO ASSOCIATION

Lessons Learned from ~1,570 Subjects treated in Nivolumab studies

The majority of treatment-related AEs are manageable with drug interruption ± corticosteroid and reversible

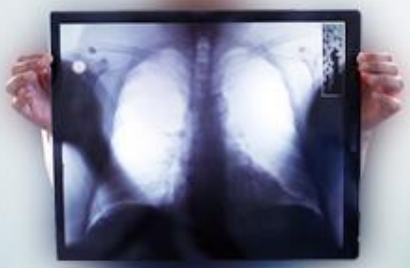
Remember !
1. Early recognition and consideration may mitigate severe toxicity ⇒ Patient education
2. Refer to specific algorithms (Protocol / Investigator Brochure) • Endocrinopathy • Hepatic Toxicity • GI Toxicity • Renal Toxicity • Pulmonary Toxicity • Skin Toxicity • Neurological Toxicity

Diferential Diagnosis

Infectious pneumonia[1]	▪ Sudden onset, rapid illness progression ▪ Productive cough and fever ▪ Clinical manifestation can differ according to the etiological agent
Chronic obstructive pulmonary disease (COPD)[2]	▪ Midlife onset; slow progression ▪ History of exposure to noxious particles ▪ Dyspnea ▪ Airflow limitation
Congestive heart failure[2,3]	▪ Fine basilar crackles on auscultation ▪ Dilated heart on chest radiography ▪ Pulmonary edema ▪ Volume restriction, not airflow limitation
Chemotherapy- and/or drug-induced pneumonitis[4]	▪ Temporal association with exposure to causative agent and development of respiratory signs and symptoms
Radiation-induced pneumonitis[5]	▪ Lung fibrosis usually confined to radiation port
Tumor progression	▪ Typically associated with radiographic changes

Immune-mediated pneumonitis

- Symptoms are nonspecific and can be difficult to distinguish from other etiologies
- Diagnosis is mainly one of exclusion and requires meticulous ruling out of all other possible etiologies

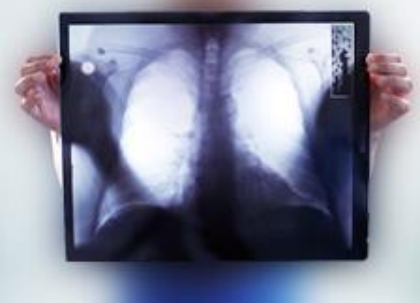


The relevant clinical study protocol should always be consulted for specific study-related information.

1. Fishman MC, et al. *Pulmonary disease*. In: Fishman MC, Hoffman AR, Klausner RD, Thaler MS, eds. Medicine. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002.
2. Celli BR, et al. *Am J Respir Crit Care Med*. 2015;191(7):e4-e27.
3. Price DB, et al. *Mayo Clin Proc*. 2010;85(12):1122-1129.
4. Matsuno O. *Respir Res*. 2012;13:39.
5. Choi YW, et al. *Radiographics*. 2004;24(4):985-997.

Tests to Confirm the Diagnosis

Imaging: Chest x-ray and CT scan[1,2]	▪ Ground-glass opacities (GGO); often seen in lung cancer patients ▪ Cryptogenic organizing pneumonia (COP)-like; commonly present in patients with melanoma ▪ Hypersensitivity-type pneumonitis ▪ Interstitial-type pneumonitis
Pulmonary function tests[3,4]	▪ Arterial oxygen saturation via oximetry ▪ Lung diffusion (DLCO) testing ▪ Spirometry
Bronchoscopy and histology	▪ Bronchoscopy with bronchoalveolar lavage and lung tissue will help distinguish infections ▪ Varied histological features[1,3,5,6]



The study-related relevant clinical study protocol should always be consulted for specific information.

1. Naidoo J. Pneumonitis with anti–PD-1/PD-L1 therapy [presentation]. ECC 2015..
2. Naidoo J, et al. ECC 2015. Abstract 503.
3. Michot JM, et al. *Eur J Cancer.* 2016;54:139-148.
4. Dosing Modification and Toxicity Management Guidelines 19 August 2016 Version.
5. Chow LQ. *Am Soc Clin Oncol Educ Book.* 2013. doi:10.1200/EdBook_AM.2013.33.e280.
6. Peng B, et al. *BMC Cancer.* 2015;15:895.

Bronchoscopy

- Bronchoscopy with bronchoalveolar lavage (BAL) is a minimally invasive, well-tolerated clinical tool
- Combined with clinical data and radiographic imaging
- Rule out other diseases (infection malignancy)
- Romagnoli *et al*., TBLB samples were considered adequate and diagnostic, and confirmed the diagnosis of DILD in 76% of the cases

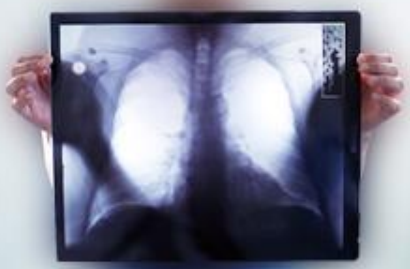
CTCAE v4.03 Definitions

Respiratory Disorders

AE[a]	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	• Asymptomatic **or** • Clinical or diagnostic observations only **or** • Intervention not indicated	• Symptomatic **or** • Medical intervention indicated **or** • Limiting instrumental ADL[b]	• Severe symptoms **or** • Limiting self care ADL[c] **or** • Oxygen indicated	• Life-threatening respiratory compromise **or** • Urgent intervention indicated (e.g. tracheotomy or intubation)

[a]AEs have been selected based on those most commonly observed with durvalumab and tremelimumab monotherapy and combination regimens; [b]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.; [c]Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
*Grade 5 definition: death.

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events version 4.03.



1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE

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J. B. A. G. Haanen[1], F. Carbonn
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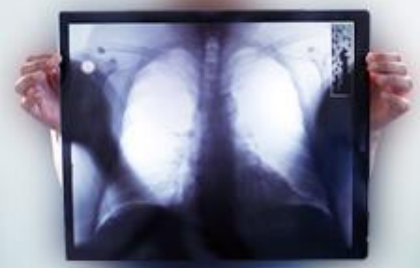
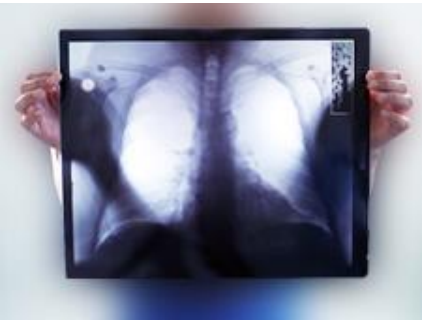


Symptom Grade	Management escalation pathway	Assessment and Investigations
Grade 1: Radiographic changes only Ground glass change, non-specific interstitial pneumonia	Consider delay of treatment Monitor symptoms every 2-3 days If worsens: treat as grade 2 or 3-4	Baseline indications: Chest X-ray Bloods (FBC/UEC/LFTs/TFTs/Ca/ESR/CRP) Consider sputum sample and screening for viral, opportunistic or specific bacterial (Mycoplasma, Legionella) infections depending on the clinical context
Grade 2: Mild/moderate new symptoms Dyspnoea, cough, chest pain	Withhold ICPi Start Ab if suspicion of infection (fever, CRP, neutrophil counts) If no evidence of infection or no improvement with Ab after 48h add in prednisolone 1 mg/kg/day orally Consider Pneumocystis prophylaxis depending on the clinical context High resolution CT +/- bronchoscopy and BAL pending appearances	Outpatient Monitoring: Monitor symptoms daily Baseline indications, as above plus: Repeat chest X-ray weekly and baseline bloods Lung function tests including TCLO If no improvement after 48h of oral prednisolone, manage as per Grade 3
Grade 3 or 4: Severe new symptoms New/worsening hypoxia Life threatening Difficulty in breathing, ARDS	Discontinue ICPi Admit patient, baseline tests as above (methyl)prednisolone i.v. 2-4 mg/kg/day High resolution CT and respiratory review +/- bronchoscopy and BAL pending appearances Cover with empiric Ab Discuss escalation and ventilation	
History: Pulmonary hypertension/respiratory disease/connective tissue disease Influenza/Mycobacterium tuberculosis exposure Smoking history Travel history Allergy history including exposure to home/occupational aeroallergens Differential Diagnosis: Pneumonia (including atypical, pneumocystis, tuberculosis) Lymphangitis Usual interstitial pneumonias Pulmonary oedema Pulmonary emboli Sarcoidosis	If not improving or worsening after 48h Add infliximab 5 mg/kg or MMF if concurrent hepatic toxicity Continue with i.v. steroids- wean as clinically indicated	Once improved to baseline: Grade 2: wean oral steroids over at least 6 weeks, titrate to symptoms Grade 3/4: wean steroids over at least 8 weeks Steroid considerations: Calcium & Vitamin D supplementation as per local guidelines Pneumocystis prophylaxis - cotrimoxazole 480 mg bd M/W/F or inhaled pentamidine if cotrim allergy

MANAGEMENT OF GRADE 1-2 PNEUMONITIS

Symptom Grade	Management escalation pathway	Assessment and Investigations
Grade 1: Radiographic changes only Ground glass change, non-specific interstitial pneumonia	Consider delay of treatment Monitor symptoms every 2-3 days If worsens: treat as grade 2 or 3-4	Baseline indications: Chest X-ray Bloods (FBC/UEC/LFTs/TFTs/Ca/ESR/CRP) Consider sputum sample and screening for viral, opportunistic or specific bacterial (Mycoplasma, Legionella) infections depending on the clinical context
Grade 2: Mild/moderate new symptoms Dyspnoea, cough, chest pain	Withhold ICPi Start Ab if suspicion of infection (fever, CRP, neutrophil counts) If no evidence of infection or no improvement with Ab after 48h add in prednisolone 1 mg/kg/day orally Consider Pneumocystis prophylaxis depending on the clinical context High resolution CT +/- bronchoscopy and BAL pending appearances	Outpatient Monitoring: Monitor symptoms daily Baseline indications, as above plus: Repeat chest X-ray weekly and baseline bloods Lung function tests including TCLO If no improvement after 48h of oral prednisolone, manage as per Grade 3



MANAGEMENT OF GRADE 3-4 PNEUMONITIS

Grade 3 or 4:
Severe new symptoms

New/worsening hypoxia

Life threatening

Difficulty in breathing, ARDS

History:
Pulmonary hypertension/respiratory disease/connective tissue disease
Influenza/Mycobacterium tuberculosis exposure
Smoking history
Travel history
Allergy history including exposure to home/occupational aeroallergens

Differential Diagnosis:
Pneumonia (including atypical, pneumocystis, tuberculosis)
Lymphangitis
Usual interstitial pneumonias
Pulmonary oedema
Pulmonary emboli
Sarcoidosis

Discontinue ICPi

Admit patient, baseline tests as above
(methyl)prednisolone i.v. 2-4 mg/kg/day

High resolution CT and respiratory review
+/- bronchoscopy and BAL pending appearances

Cover with empiric Ab

Discuss escalation and ventilation

If not improving or worsening after 48h

Add infliximab 5 mg/kg or MMF if concurrent hepatic toxicity

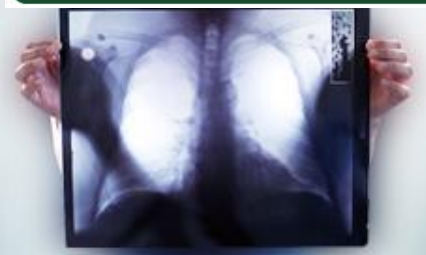
Continue with i.v. steroids- wean as clinically indicated

Once improved to baseline:
Grade 2: wean oral steroids over at least 6 weeks, titrate to symptoms

Grade 3/4: wean steroids over at least 8 weeks

Steroid considerations:
Calcium & Vitamin D supplementation as per local guidelines

Pneumocystis prophylaxis - cotrimoxazole 480 mg bd M/W/F or inhaled pentamidine if cotrim allergy



Re-Challenge ICIs after Pneumonitis

In Grade 1 and 2 pneumonitis we can re-challenge the drug with careful patient selection

Subjects with incidence of Grade 3 and 4 pneumonitis should be permanently discontinued from immunotherapy

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Total No 915

12/43 pts Re-challenge Immunotherapy

9 GR 1
Of 17pts **53%**

3 GR 2
Of 14pts **21%**

Initially Cortico-steroids p.o

Re-challenge

1 pt Relapsed **Drug Holding**

2 pts Relapsed **Corticosteroids**

Naidoo J. et al Pneumonitis in patients treated with anti PD-1/PD-L1 therapy; J Clin Oncol2016.68.2005

NCCN management of toxicity related to immunotherapies, 2016

Summarizing

- **Always look and ask for side effects,**

half of patients with pneumonitis are asymptomatic and 1/3 had negative CXR

- **Always ask for HRCT** if you suspect pneumonitis
- **Treat early proactively** even grade 2 toxicity
- **Adapt the therapy to the individual patient**
  (if grade 3 toxicity with no change in 48 hrs do not wait for 72 hrs…)
- **More combinations potentially more side effects**

- ***Education of oncologists and non-oncologists***
- ***Specialists collaborations***
- ***Education of patients for early detection of irAE***